DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022291

REVISED WRITTEN REQUEST
AMENDMENT 1

GlaxoSmithKline, LLC
Attention: Dennis Williams, Pharm.D.
Associate Director
Regulatory Affairs, Oncology
1250 South Collegeville Road
Collegeville, PA 19426

Dear Dr. Williams:

Please refer to your correspondence dated June 6, 2011, requesting changes to FDA's January 25, 2010 Written Request for pediatric studies for Promacta® (eltrombopag) Tablets.

We have reviewed your proposed changes and are amending the below-listed sections of the Written Request. All other terms stated in our Written Request issued on January 25, 2010 remain the same. (Text added is underlined. Text deleted is strikethrough.)

Type of studies:
Study 1: Pharmacokinetic/Pharmacodynamic (PK/PD) and Safety Study
Study 2: Efficacy, PK and Safety Study

These studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. ~~If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.~~

Objective of each study:
Study 1: To characterize the PK/PD ~~profile~~ and collect data on the safety and tolerability of eltrombopag during a 12 week treatment period in children with chronic ITP.

Study 2: To assess the efficacy of eltrombopag as add-on therapy to standard treatment in achieving a target platelet count and to describe the pharmacokinetics ~~PK profile~~, safety and tolerability of eltrombopag during a ~~24~~ 12 week randomized treatment period followed by a 24 week open-label treatment period in children with chronic ITP.

Age group in which study will be performed:
Study 1 and Study 2:
Pediatric patients 2 years to < 17 years at study entry divided into three age cohorts

Cohort 1: age 12 years to < 17 years
Cohort 2: age 6 years to < 12 years
Cohort 3: age 2 years to < 6 years

For Study 1, Cohort 1 data must be reviewed and found acceptable by the Agency prior to enrolling patients in Cohort 2. Similarly, Cohort 2 data must be reviewed and found acceptable by the Agency prior to enrolling patients in Cohort 3.

Number of patients to be studied:
Study 2: The youngest cohort must enroll and treat at least 12 patients. Each of the older cohorts must enroll and treat at least 25 patients. Overall there must be at least 75 patients enrolled and treated in the study. ~~The number of patients should be distributed approximately evenly over the three age cohorts to the extent possible, given the incidence of disease.~~ The study must include a sufficient number of patients to detect a pre-specified, clinically meaningful effect (all ages combined) on the primary endpoint.

The clinical study safety database (Study 1 and Study 2) must include at least ~~250~~ 130 pediatric patients exposed to eltrombopag to characterize the safety of the drug, with the duration of eltrombopag treatment at least 24 weeks in at least ~~188~~ 100 patients. All patients must be followed for safety for 4 weeks after discontinuation of study treatment.

Study design:
Study 2: Randomized, double-blind, placebo-controlled trial in which eltrombopag is administered as add-on therapy to standard treatment for at least ~~24~~ 12 weeks treatment duration. ~~At least 188 p~~ Patients will complete a 24 week open-label treatment period and 4 week follow-up period. All patients must be followed for safety for 4 weeks after discontinuation of study treatment. Sparse PK samples must be collected to support exposure-response analysis.

Study endpoints:
Pharmacokinetic and Exposure-Response (Study 1 and Study 2)
Plasma eltrombopag pharmacokinetic parameters from Study 1 must include AUC(0-t), Cmax, Ct, Vd/F and CL/F. Data from relevant studies, including Study 1 and Study 2, must be combined to develop exposure-response for safety and effectiveness endpoints. The goals of these analyses are: a) to provide supportive evidence of effectiveness; and b) to support the dosing recommendations.

Efficacy/Pharmacodynamic
The primary efficacy endpoint (Study 2) ~~must be~~ will be the proportion of patients in a group achieving ~~and maintaining~~ a platelet count ~~of~~ ≥50,000/mcl for ~~the last~~ any 6 of the last 8 weeks ~~of treatment~~ (5 through 12) during the 12 week randomized treatment period. ~~during the study~~

Secondary endpoints will include the following, with Day 1 being the first day of treatment.

- *Proportion of patients achieving a platelet count of >50,000/mcl at least once during the 12 week treatment period.*
- *Weighted mean platelet change (area under the platelet-time curve divided by duration) from baseline to ~~day 168~~ week 12.*

Safety:
~~The data from the relevant studies must be combined to develop exposure-response for safety and effectiveness endpoints. The goals of these analyses are: a) to provide supportive evidence of effectiveness; and b) to support the dosing recommendations~~.

Drug information:
In Study 1, d ~~D~~osing selected for Cohorts 2 and 3 ~~may be adjusted based on~~ must be supported by the results from the older age cohort and dosing in Study 2 must be supported by the results in Study 1. Dosing adjustments also must be based on platelet count and must follow labeled instructions. Dosing in all age groups must be adjusted to maintain platelet counts between 50,000-200,000/mcl.

Statistical information, including power of study and statistical assessments:
For such binary outcomes, we recommend using a Cochran-Mantel-Haenszel test as the primary analysis. One analysis should treat missing outcomes as failures. Every subject should be accounted for in the analysis by either being measured for the primary endpoint or properly accounted for if not measured for the primary endpoint. The number of subjects not measured for the primary endpoint should be kept to a minimum. Too much missing data undermine the reliability and confidence of the results.

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated January 25, 2010, as amended by this letter, must be submitted to the Agency on or before December 4, 2015 in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a new drug application (NDA) / supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. In addition, send a copy of the cover letter of your submission, via fax (240-276-9327) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

If you have any questions, call Mara Miller, Regulatory Project Manager, at (301) 796-0683.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Specific Study Requirements

Type of studies:
Study 1: Pharmacokinetic/Pharmacodynamic (PK/PD) and Safety Study
Study 2: Efficacy, PK and Safety Study

These studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities.

Indication to be studied: Treatment of thrombocytopenia in children with chronic ITP who:

1) are at risk for bleeding; and
2) are refractory to ITP therapy, have relapsed after at least one prior ITP therapy, or are not eligible for other ITP treatments.

Objective of each study:
Study 1: To characterize the PK/PD and collect data on the safety and tolerability of eltrombopag during a 12 week treatment period in children with chronic ITP.

Study 2: To assess the efficacy of eltrombopag as add-on therapy to standard treatment in achieving a target platelet count and to describe the pharmacokinetics, safety and tolerability of eltrombopag during a 12 week randomized treatment period followed by a 24 week open-label treatment period in children with chronic ITP.

Age group in which study will be performed:
Study 1 and Study 2:
Pediatric patients 2 years to < 17 years at study entry divided into three age cohorts
Cohort 1: age 12 years to < 17 years
Cohort 2: age 6 years to < 12 years
Cohort 3: age 2 years to < 6 years

For Study 1, Cohort 1 data must be reviewed and found acceptable by the Agency prior to enrolling patients in Cohort 2. Similarly, Cohort 2 data must be reviewed and found acceptable by the Agency prior to enrolling patients in Cohort 3.

Number of patients to be studied:
Study 1: The study must be prospectively powered to target a 95% CI within 60% and 140% of the point estimate for the geometric mean estimates of clearance and volume of distribution for eltrombopag in each age group.

Study 2: The youngest cohort must enroll and treat at least 12 patients. Each of the older cohorts must enroll and treat at least 25 patients. Overall there must be at least 75 patients enrolled and treated in the study. The study must include a sufficient number of patients to detect a pre-specified, clinically meaningful effect (all ages combined) on the primary endpoint.

The clinical study safety database (Study 1 and Study 2) must include at least 130 pediatric patients exposed to eltrombopag to characterize the safety of the drug, with the duration of

eltrombopag treatment at least 24 weeks in at least 100 patients. All patients must be followed for safety for 4 weeks after discontinuation of study treatment.

Study design:
Studies 1 and 2: Patients will have a confirmed diagnosis of chronic ITP according to the American Society of Hematology/British Committee for Standards in Haematology (ASH/BCSH) guidelines (George, 1996; BCSH, 2003). In addition, a peripheral blood smear and bone marrow examination must support the diagnosis of ITP with no evidence of other causes of thrombocytopenia.

Study 1: Single-arm, open-label study starting with Cohort 1. Blood samples for PK must be collected at steady state. Timing of blood samples must be such that the entire time course of plasma concentrations can be adequately captured for the entire population. Blood sampling must be age appropriate. PK estimates in the 12 to 17 year age group must be used to inform study design and minimize blood draw volumes in the younger age groups. Safety, PK, and platelet count data from Study1 must be reviewed-in each cohort to contribute to the confirmation or modification of the starting dose and dosing strategy for that cohort in Study 2. Safety, PK, and platelet count data from Study 1 also must be reviewed and determined to be acceptable in the older cohort(s) prior to enrolling subjects from the younger cohort(s).

Study 2: Randomized, double-blind, placebo-controlled trial in which eltrombopag is administered as add-on therapy to standard treatment for at least 12 weeks treatment duration. Patients will complete a 24 week open- label treatment period and 4 week follow-up period. All patients must be followed for safety for 4 weeks after discontinuation of study treatment. Sparse PK samples must be collected to support exposure-response analysis.

Study endpoints:
Pharmacokinetic and Exposure-Response (Study 1 and Study 2)

- Plasma eltrombopag pharmacokinetic parameters from Study 1 must include AUC(0-t), Cmax, Ct, Vd/F and CL/F. Data from relevant studies, including Study 1 and Study 2, must be combined to develop exposure-response for safety and effectiveness endpoints. The goals of these analyses are: a) to provide supportive evidence of effectiveness; and b) to support the dosing recommendations.

Efficacy/Pharmacodynamic

- The primary efficacy endpoint (Study 2) will be the proportion of patients in a group achieving a platelet count ≥50,000/mcl for any 6 of the last 8 weeks (5 through 12) during the 12 week randomized treatment period.

Secondary endpoints will include the following, with Day 1 being the first day of treatment.

- Proportion of patients achieving a platelet count of ≥50,000/mcl at least once during the 12 week treatment period.
- Proportion of patients with platelet counts ≥50,000/mcl during treatment with eltrombopag in: ≥ 60% of assessments between days 15 and 168.

- Weighted mean platelet change (area under the platelet-time curve divided by duration) from baseline to week 12.
- Maximum period of time with platelet count continuously ≥50,000/mcl during the 24 weeks of eltrombopag dosing.
- Proportion of patients achieving platelet counts ≥50,000/mcl at anytime during the 24 weeks of eltrombopag dosing.
- Proportion of patients that reduced or discontinued baseline concomitant ITP medications while receiving eltrombopag during the 24 week study period.
- Proportion of patients that required protocol defined rescue treatment during the study.
- Reduction of bleeding symptoms associated with ITP based on the WHO bleeding scale.

Safety

- Safety and tolerability parameters must include blood pressure, respiratory and heart rate, ocular examinations to evaluate for cataracts (slit lamp examination), clinical laboratory assessments (including but not limited to: baseline and weekly CBC, liver function tests, serum creatinine, and urinalysis; and data from bone marrow biopsy if done) and frequency of all adverse events.

Data Monitoring Committee:
A Data Monitoring Committee (DMC) must be utilized during the conduct of these studies to identify safety issues warranting modification or interruption of study procedures, particularly for the younger age cohorts. The DMC must have a formal charter that describes its composition and scope and the procedures by which it will abide.

Drug information:

- Dosage form: age-appropriate formulations. The relative bioavailability between the tablet and suspension formulations must be established in a manner consistent with the guidance "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products"- General Considerations" (http://www .fda.gov /downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm07023 9).
- Route of administration: oral
- Regimen:
  - Cohort 1 (age 12 to < 17 years): The starting dose will be 25 mg once daily.
  - Cohort 2 (age 6 to < 12 years): The starting dose will be 0.7 mg/kg once daily.
  - Cohort 3 (age 2 to < 6 years): The starting dose will be 0.7 mg/kg once daily.

  - For patients of East Asian ancestry the starting dose will be as follows.
    Cohort 1 (age 12 to < 17 years): The starting dose will be 12.5 mg once daily.
    Cohort 2 (age 6 to < 12 years): The starting dose will be 0.5 mg/kg once daily.
    Cohort 3 (age 2 to < 6 years): The starting dose will be 0.5 mg/kg once daily.

In Study 1 dosing selected for Cohorts 2 and 3 must be supported by the results from the older age cohort and dosing in Study 2 must be supported by the results in Study 1. Dosing adjustments also must be based on platelet count and must follow labeled instructions. Dosing in all age groups must be adjusted to maintain platelet counts between 50,000-200,000/mcl.

Use an age-appropriate formulation in the study(ies) described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

If 1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives marketing approval), 2) the Agency publishes the exclusivity determination notice required under section 505A(e)(l) of the Act, and 3) you have not marketed the formulation within one year after the Agency publishes such notice, the Agency will publish a second notice reflecting the fact that the approved pediatric formulation has not been marketed, in accordance with section 505A(e)(2).

If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients.

Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

- Drug specific safety concerns: Hepatotoxicity, reticulin fiber deposition within the bone marrow, thrombotic/thromboembolic complications, malignancy, cataracts, renal toxicity, hemorrhage following discontinuation of eltrombopag.

Statistical information, including power of study and statistical assessments:

Study 1: The study must be prospectively powered to target a 95% CI within 60% and 140% of the point estimate for the geometric mean estimates of clearance and volume of distribution for eltrombopag in each age cohort. The final study report must provide appropriate analyses and descriptive statistics for all PK data. Descriptive statistics must also be presented for safety and PD/effectiveness data.

Study 2: The protocol must provide a statistical analysis plan for assessing efficacy and safety. The null hypothesis of no difference between treatment groups will be tested using an alpha level of 5% (two-sided). The study must provide at least 80% power to detect a pre-specified, clinically meaningful effect on the primary endpoint. The primary analysis method should be pre-specified including any covariates to be included in the statistical model. You should stratify the primary endpoint analysis by age cohort. The primary analysis population should be the intent to-treat population consisting of all randomized patients with any on-treatment primary

endpoint data. One or more sensitivity analyses of the primary endpoint to assess the impact of missing data should be pre-specified. The statistical analysis plan must be submitted and receive division concurrence prior to the start of the study.

For such binary outcomes, we recommend using a Cochran-Mantel-Haenszel test as the primary analysis. One analysis should treat missing outcomes as failures. Every subject should be accounted for in the analysis by either being measured for the primary endpoint or properly accounted for if not measured for the primary endpoint. The number of subjects not measured for the primary endpoint should be kept to a minimum. Too much missing data undermine the reliability and confidence of the results.

Labeling that may result from the study(ies): You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that eltrombopag olamine (SB-4971 15-GR) is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).

Format and types of reports to be submitted: You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. These postmarketing adverse event reports should be submitted as narrative and tabular reports.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the FDA website at http://www.fda.gov/CDER/REGULATORY/ersr/Studydata.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072349.pdf.

Timeframe for submitting reports of the study(ies): Reports of the above studies must be

submitted to the Agency on or before December 4, 2015. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

Response to Written Request: Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

Furthermore, if you agree to conduct the study(ies), but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RICHARD PAZDUR
11/23/2011